DOCKET NO.: ISIS-5299 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Buchardt, *et al.***	Confirmation No.: **5682**
Serial No.: **10/691,012**	Group Art Unit: 1631
Filing Date: **October 22, 2003**	Examiner: **Michael L. Borin**
For: **Peptide Nucleic Acids**	

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 41.37

This brief is being filed in support of Appellant's appeal from the rejections of claims 34-36, 38-41, 43-45, and 47-73 dated November 6, 2008. A Notice of Appeal was filed on February 19, 2009.

1. REAL PARTY IN INTEREST

Based on information supplied by Appellants and to the best of the undersigned's knowledge, the real parties in interest in the above-identified patent application are Ole Buchardt (deceased), Michael Egholm, Peter Eigil Nielsen and Rolf Henrik Berg. ISIS Pharmaceuticals, Inc., a corporation of Delaware, a licensee of the parties Buchardt, Egholm, Nielsen and Berg, is joined with them in prosecuting the above-identified application.

2. RELATED APPEALS AND INTERFERENCES

Based on information supplied by Appellants and to the best of the undersigned's knowledge, there are no other appeals or interferences known to Appellants or Appellants' legal representative, or the assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal. Appellants note that the appealed

claims were added for the purpose of provoking an interference with U.S. Patent No. 6,472,209, issued on October 29, 2002.

3. STATUS OF CLAIMS

Claims 34-36, 38-41, 43-45, and 47-73 are under final rejection. A listing of the claims involved in the Appeal are listed in the appendix entitled CLAIMS APPENDIX.

4. STATUS OF AMENDMENTS

There were no amendments filed after the final rejection.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The following summary is for the purpose of complying with the provisions of 37 CFR 41.37(c)(1)(v). The entire disclosure should be reviewed to obtain a complete understanding of the claim language.

The present invention concerns methods of *in vivo* treatment of living cells by extracellularly administering to the cells a polyamide nucleic acid oligomer containing neutral amide backbone linkages which is complementary to a target nucleic acid (Claim 33, page 17, line 28 to page 19, line 3). The administration is performed under conditions where the oligomer engenders a biological response associated with the target in a sequence specific manner. *Id.* The methods can comprise additionally detecting the biological response (Claim 41, page 18, lines 4-6). Other aspects of the invention concern methods where the oligomer engenders a biological response associated with the target in a sequence specific manner (Claim 48, page 17, line 28 to page 19, line 3) and where such a response is detected (Claim 58, page 18, lines 4-6).

The invention also concerns methods comprising administering to a organism a polyamide nucleic acid oligomer that contains neutral amide backbone linkages and is complementary to a target nucleic acid, under conditions wherein the oligomer specifically

binds to DNA or RNA deriving from a gene in the organism (Claim 65, page 17, line 28 to page 19, line 3).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues on appeal are:

(1) whether claims 34-36, 48-51, 58, 59, and 65-68 are anticipated under 35 U.S.C. § 102(e) by U.S. Patent No. 5,142,047 ("the Summerton patent"); and

(2) whether the specification would have enabled practice of claims 34-36, 38-41, 43-45, and 47-73 under 35 U.S.C. § 112, first paragraph.

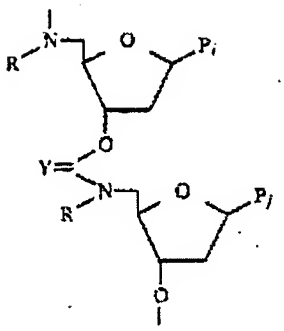
7. ARGUMENT

Alleged Anticipation

Claims 34-36, 41, 48-51, 58, 59, and 65-68 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,142,047 ("the Summerton patent"). This rejection is improper because the Summerton patent is alleged to be relevant for its disclosure of compounds that have a different structure than those recited in the instant claims.

For a reference to be anticipatory, it must describe "all elements of [the] claimed invention arranged as in that claim." *Carella v. Starlight Archery*, 804 F.2d 135, 138 (Fed. Cir. 1986); *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1267 (Fed. Cir. 1991). Importantly, for a rejection to be proper under 35 U.S.C. § 102, the reference must "clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *In re Arkley*, 172 U.S.P.Q. 524, 526 (C.C.P.A. 1972) (emphasis in original).

The Summerton patent does not satisfy these requirements. The Examiner asserts that the linkages recited in the instant claims correspond to the linkage used in the following compound in the Summerton patent (November 6, 2008, Final Rejection at pages 8-10).



However, this linkage (*i.e*, -**O**-C(=O)-NR- when Y is oxygen) is a carbamate linkage (a derivative of a carbonic acid), whereas the rejected claims recite an amide linkage (*i.e.*, -**C**-C(=O)-NR-) (a derivative of a carboxylic acid). Thus, there is no anticipation.

When Appellant brought this distinction to the Examiner's attention, the Examiner asserted that if one ignores the non-carbonyl oxygen atom in the –O-CO-NR- linkage, "the reference is viewed as containing the neutral amide linkage (underlined) as instantly claimed." (Final Rejection at pages 9-10). Such an interpretation, however, is not consistent with the understanding of a person skilled in the art. Those skilled in the art regard the "ignored" oxygen atom as integral to the structure of a carbamate group. Moreover, those skilled in the art would not simply ignore a functional atom in analyzing the linkage, at least because whether there is an oxygen, nitrogen, or carbon atom adjacent to the CO-NR- group impacts electronic properties and is important to the nature of the group. A person skilled the art would not ignore the disputed oxygen atom (and view the remaining –CO-NR- portion of –O-CO-NR- as an amide) any more than they would also ignore the NR group (and view the remaining –O-CO- portion of –O-CO-NR- as an ester).

Additionally, in ignoring the oxygen atom of the Summerton structure the Examiner gives no indication of the fate of the pair of electrons that bond between the oxygen atom and the carbon atom of the carbonyl radical. If the pair of electrons are removed with the oxygen atom (after all oxygen is more electro negative that carbon) a carbocation results. Of course a carbocation has a net positive charge. A net positive charge is not neutral as is required by the claims at issue. If the pair of electrons is left with the carbon atom of the carbonyl group a carbanion results. Such carbanion has a net negative charge. A net negative charge is also not neutral as is required by the claims at issue.

The Summerton patent also refutes the Examiner's position that the oxygen atom can be ignored. The structure reproduced in the final Office Action is found in column 5 of the Summerton patent, and is designated as structure "B-B". In column 6, lines 49-51, the

Summerton patent refers to B-B as a carbamate-linked structure, not an amide-linked structure.

Because the structure that the Summerton patent discloses is different from that recited in the instant claims, the rejection for alleged anticipation is improper and should be withdrawn.

Alleged Lack of Enablement

Claims 34-36, 38-41, 43-45, and 47-73 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Appellants request that this rejection be withdrawn because there is no dispute that those skilled in the art would have been able to practice the recited methods to at least some measurable extent.

Claims 34-36, 38-41, 43-45, and 47-73 are directed to methods for administering polyamide nucleic acids to cells. The Examiner has rejected these claims because those skilled in the art allegedly would encounter difficulty in getting the polyamide nucleic acids to traverse cell membranes. Specifically, the Examiner has expressed concern as to whether such compounds "administered in vivo will be capable to exert the same effect as observed *in vitro* [in a] cell-free environment" and whether the instant specification provides "guidance of the dosages and regimes that would enable PNAs to get across cell membranes under *in vivo* conditions" (Final Rejection at page 4). The Examiner cites three references in support of the rejection (*id.*). Significantly, however, none of the references are said to demonstrate that the claimed compounds are not taken up by cells; rather, they are said to demonstrate that those skilled in the art encountered difficulties and/or inefficiencies when they worked on getting such compounds to be taken up by cells. The Examiner, for example, relies upon U.S. 6,472,209 for its disclosure that "PNA oligomers ... have low phospholipid membrane permeability ... and have been reported to be taken up by cells very poorly" (*id.*).

Thus, there is no dispute that those skilled in the art would have been able to practice the claimed methods to at least some measurable extent. Although the Examiner has questioned how efficient practice of the claimed methods would have been, not only has the Examiner not identified any legal authority supporting rejection of claims on this basis, but the relevant authority is directly to the contrary. *Engel Industries, Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 ("[t]he enablement requirement is met if the description enables any mode of making and using the claimed invention."); *CFMT, Inc. v. Yieldup International Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003) (claims directed to "cleaning" semiconductor

wafers held to be enabled so long as those skilled in the art could achieve any level of cleaning with the claimed invention without undue experimentation).

In fact, a review of the state of the art as of Applicants' effective filing date – as demonstrated by references already of record -- shows that those skilled in the art had considerable experience with techniques for uptake of the recited compounds. Applicants draw the Board's attention to Uhlmann, *et al.*, *Angew. Chem. Int. Ed.* 1998, 37, 2796-2823 (hereinafter, "the Uhlmann article", a copy of which was previously submitted to the Office). The Uhlmann article describes techniques for allowing PNAs to bypass the membrane barrier via microinjection or use of detergents. *See*, Section 5.2 on page 2816. One of the microinjection references cited in the Uhlmann article dates from 1993 and other references date from the mid-1990s. *See*, Section 5.2 on page 2816 of the Uhlmann article. Thus, knowledge concerning delivery of PNAs at the time of the instant application was considerably more advanced than acknowledged by the Examiner. Further, Applicants note that the Uhlmann article is a review article, and point the Board's attention to Hanvey, Science 1992, 258, 1481-1485 ("the Hanvey publication"), which is reference 97 in the Uhlmann article. It is clear from the Hanvey publication that microinjection was used for introducing PNA in to cell in 1992, *i.e.* prior to the filing date of the parent application. In light of this information, Applicants' disclosure is more than adequate, and would not require undue experimentation to practice the instant inventions.

Because there is no dispute that those skilled in the art would have been able to practice the claimed methods (and, in fact, contemporaneous supporting evidence of record), the rejection for alleged lack of enablement is improper and should be withdrawn..

Date: April 3, 2009

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8. CLAIMS APPENDIX

34. A method of treating living cells, said method comprising extracellularly administering to said cells a polyamide nucleic acid oligomer containing neutral amide backbone linkages which is complementary to a target nucleic acid, under conditions wherein said oligomer engenders a biological response associated with said target in a sequence specific manner, said administration being in vivo.

35. The method of claim 34, wherein said method comprises detecting said biological response.

36. The method of claim 34, wherein said cells are within a mammal.

38. The method of claim 34, wherein said biological response is a modification of polypeptide expression.

39. The method of claim 38, wherein said modification is a reduction in polypeptide expression.

40. The method of claim 34, wherein said biological response is characterized by a physiological change in a living organism.

41. A method of treating a mammal, said method comprising:

a) extracellularly administering to said mammal a polyamide nucleic acid oligomer containing neutral amide backbone linkages, which is complementary to a target nucleic acid,

under conditions wherein said oligomer engenders a biological response associated with said target in a sequence specific manner, and

b) detecting said biological response.

43. The method of claim 41, wherein said biological response is a modification of polypeptide expression.

44. The method of claim 43, wherein said modification is a reduction in polypeptide expression.

45. The method of claim 41, wherein said biological response is characterized by a physiological change in said mammal.

47. The method of claim 41, wherein said administration is an intraperitoneal administration.

48. A method comprising administering to living cells in vivo a polyamide nucleic acid oligomer that contains neutral amide backbone linkages and is complementary to a target nucleic acid, under conditions wherein said oligomer engenders a biological response associated with said target in a sequence specific manner.

49. The method of claim 48, wherein said method comprises detecting said biological response.

50. The method of claim 48, wherein said cells are within a mammal.

51. The method of claim 48, wherein said oligomer has sequence specificity for a nucleic acid sequence that regulates the expression of or encodes a polypeptide.

52. The method of claim 51 wherein said polypeptide participates in cell signaling.

53. The method of claim 48, wherein said biological response is a modification of polypeptide expression.

54. The method of claim 53, wherein said modification is a reduction in polypeptide expression.

55. The method of claim 48, wherein said biological response is characterized by a physiological change in a living organism.

56. The method of claim 48, wherein said administration is an intraperitoneal administration.

57. The method of claim 48, wherein said administration is extracellular.

58. A method comprising:

administering to a mammal a polyamide nucleic acid oligomer that contains neutral amide backbone linkages and is complementary to a target nucleic acid, under conditions wherein said oligomer engenders a biological response associated with said target in a sequence specific manner, and

detecting said biological response.

59. The method of claim 58, wherein said oligomer has sequence specificity for a nucleic acid sequence that regulates the expression of or encodes a polypeptide.

60. The method of claim 59, wherein said polypeptide participates in cell signaling.

61. The method of claim 58, wherein said biological response is a modification of polypeptide expression.

62. The method of claim 61, wherein said modification is a reduction in polypeptide expression.

63. The method of claim 58, wherein said biological response is characterized by a physiological change in said mammal.

64. The method of claim 58, wherein said administration is an intraperitoneal administration.

65. A method comprising administering to a organism a polyamide nucleic acid oligomer that contains neutral amide backbone linkages and is complementary to a target nucleic acid, under conditions wherein said oligomer specifically binds to DNA or RNA deriving from a gene in said organism.

66. The method of claim 65 further comprising detecting expression of said gene following said administration.

67. The method of claim 65 wherein said organism is a mammal.

68. The method of claim 65 wherein said DNA or RNA regulates the expression of or encodes a polypeptide.

69. The method of claim 68 wherein said polypeptide participates in cell signaling.

70. The method of claim 65 wherein said administration modifies polypeptide expression in said organism.

71. The method of claim 70 wherein said modification is a reduction in polypeptide expression.

72. The method of claim 65 wherein said administration is an intraperitoneal administration.

73. The method of claim 65 wherein said administration produces a biological response in said organism.

9. EVIDENCE APPENDIX

There is no additional evidence provided.

10. RELATED PROCEEDINGS APPENDIX

Applicants are not aware of any related proceedings.